## REMARKS

**Amendments**

Claims 38 and 39 have been incorporated in claim 37 and therefore are cancelled as moot. Claims 47 and 48 have been incorporated in claim 45 and hence are cancelled as moot. Claims 37 and 45 have been amended to recite the lower limit of 80mg/mL as recited in claim 49. In that the amendments do not introduce new matter, entry thereof is respectfully requested.

**Section 103 - Presta and Coval**

Claims 37-39, 44 and 45 are rejected under 35 USC Section 103 as being unpatentable over US Patent No. 5,965,709 (Presta) in view of US Patent No. 4,093,606 (Coval).

This rejection is obviated by the amendment of claims 37 and 45 herein to recite the lower limit of 80mg/mL as in claim 49, which claim is not rejected over this art. Reconsideration and withdrawal of the rejection is respectfully requested.

**Section 103 - Presta, Coval and Chang 1**

Claims 37-39, 44 and 45 are rejected under 35 USC Section 103 as being unpatentable over Presta in view of Coval and US Patent No. 5,614,611 (Chang 1).

This rejection is obviated by the amendment of claims 37 and 45 herein to recite the lower limit of 80mg/mL as in claim 49, which claim is not rejected over this art. Reconsideration and withdrawal of the rejection is respectfully requested.

**Section 103 - Davis, Arakawa, Coval, and Cleland**

Claims 37-39 and 44-49 are rejected under 35 USC Section 103 as being unpatentable over Davis *et al. Springer Semin. Immunopathol.* 15: 51-73 (1993) in view of US Patent No. 5,783,186 (Arakawa), Coval, and Cleland *et al. Proceed. Intern. Symp. Control. Rel. Bioact. Mater* 22:514-515 (1995).

Davis is said to teach administration of an anti-IgE antibody to humans to treat allergic diseases, the administration resulting in achievement of an initial plasma concentration of from 1 µg/ml, to effect binding to circulating IgE and an initial plasma concentration of 10-100 µg/ml to effect binding to

IgE-producing B cells. Davis is cited as teaching that a 30 mg IV dose of the anti-IgE antibody CGP 51901 would be the estimated amount of antibody to achieve the former initial plasma concentration and by extension, a minimum of a 300mg dose would achieve the latter initial plasma concentration.

The Examiner acknowledges that Davis does not teach either the concentration of the anti-IgE antibody, nor SQ administration.

Arakawa is said to disclose administration of monoclonal antibodies to humans may be SQ, IV or IM and may be a single bolus injection. Arakawa is said to further teach that the amount of the antibody to be used will "vary depending on the nature and severity of the condition but in general will range from about 0.1µg/kg body weight to about 100mg/kg body weight, i.e. about 70mg in a normal size adult, more in a heavier adult."

Coval is relied on for disclosing a reconstituted formulation of antibody for use in treating infection in a mammal, including humans, the antibody in an amount of 50mg/mL (5%).

Cleland is said to teach a method for providing increased stability of proteins using trehalose during lyophilization and protein concentrations of 134 mg/mL or 400 mg/mL.

Applicants submit that the presently claimed invention is patentable over the cited art.

**THE PRESENT INVENTION**

The claims as pending herein concern treating a patient by administering subcutaneously a formulation to the patient in order to treat an IgE-mediated allergic disease in the patient, wherein the formulation comprises an antibody which binds IgE in an amount of at least 80 mg/mL.

The inventors of the present applications first recognized the desirability of such high anti-IgE antibody concentrations for SQ administration, something which was not taught for an anti-IgE antibody formulation in the cited art. Moreover, the inventors developed a high concentration anti-IgE antibody formulation that was, surprisingly, stable in spite of the high antibody concentration in it, and, moreover, safe and effective for SQ administration to patients for treating IgE-mediated allergic diseases. See, especially,

Example 2 on pages 37-43.

Applicants will demonstrate below that the cited art would not have suggested the claimed invention, prior to the filing of the present application.

**THE CITED ART**

Davis concerns the CG9 51901 anti-IgE antibody. This reference is completely silent as to SQ administration of the CG9 51901 antibody, formulating the CG9 51901 antibody for SQ administration, let alone a formulation comprising an anti-IgE antibody in an amount of at least 80 mg/mL.

Arakawa concerns the mAb74 anti-HER2 antibody which induces apoptosis and its use to treat HER2 overexpressing cancer, rather than therapy of an IgE-mediated allergic disease with an anti-IgE antibody. Aside from a passing reference to *Remington's Pharmaceutical Sciences* (1990) (col. 6, lines 45-46), Arakawa lacks detailed guidance as to formulating the mAb74 antibody, let alone how to generate a stable formulation with a high antibody concentration as claimed herein.

Coval refers to a 50mg/mL gamma globulin composition. The reliance on Coval is believed to be mooted by the amendment of claims 37 and 45 herein to replace "50mg/mL" with "80mg/mL."

Cleland is concerned with generating a controlled release formulation where the drug that is formulated is either recombinant human growth hormone (rhGH) or recombinant human interferon-γ (rhIFN-γ). rhGH and rhIFN-γ are distinct from an anti-IgE antibody, and are used to treat different indications from the presently claimed IgE-mediated allergic disease. Cleland does not discuss SQ administration of the rhGH or rhIFN-γ formulations.

**THE PRESENTLY CLAIMED INVENTION IS NONOBVIOUS OVER THE CITED REFERENCES**

Applicants submit that the cited art would not have rendered obvious the presently claimed invention at the time of filing the present application.

The only cited reference that concerns therapy with an anti-IgE antibody is Davis but, as acknowledged by the Examiner, that reference does not teach an antibody concentration of 80 mg/mL to about 400mg/mL, nor does it teach SQ administration of the antibody. The reference does not suggest anywhere such aspects of the presently claimed invention.

The other references - Arakawa, Coval, and Cleland fail to supply the deficiencies of Davis.

In particular, since Arakawa is concerned with a completely different antibody (anti-HER2 antibody vs. anti-IgE antibody as in the present claims) and a totally different therapy (HER2 overexpressing cancers cF. IgE-mediated allergic disease as claimed herein), Applicants submit the skilled person would not turn to the disclosure of Arakawa when determining how to practice the presently claimed method. The patent office has previously taken the position that methods for treating "different diseases which have different pathologies, etiologies, symptoms and prognoses" are patentably distinct (Paper #4, last lines on pg. 2). Hence, any teaching in Arakawa concerning HER2 overexpressing cancer with different pathology, etiology, symptoms and prognosis from IgE-mediated allergic disease as claimed herein, would not render obvious the claimed method. In any event, as noted above, Arakawa contains no enabling guidance as to how to generate a high antibody concentration formulation as presently set forth in the claims herein, and for this further reason, the combination of Davis and Arakawa (even if the disclosures would have been combined) would not lead to the presently claimed invention.

Coval does not disclose or suggest how to generate an anti-IgE antibody formulation comprising the antibody in an amount in the range from 80mg/mL to about 400mg/mL, nor is SQ administration of such a formulation taught or alluded to therein. Hence, the combination of Davis and Coval would also fail to render obvious the presently claimed invention.

Turning now to Cleland, since the proteins therein (rhGH and rhIFN-γ) are different in molecular weight, structure and function from an antibody, namely an anti-IgE antibody, Cleland is not predictive as to the ability to generate a stable anti-IgE antibody formulation. Moreover, since rhGH and rhIFN-γ are used to treat diseases which have different pathologies, etiologies, symptoms and prognoses from IgE-mediated allergic disease as claimed herein, Applicants submit that Cleland would not render obvious the presently claimed therapeutic method. In addition, since Cleland does not refer to SQ administration of the rhGH or rhIFN-γ formulations, it fails to supply a further deficiency of Davis.

Hence, Applicants submit that, even when combined, the references would not

have rendered obvious the presently claimed invention at the time of filing.

Even assuming for argument's sake that by combining the teachings of the references the skilled person would have arrived at the presently claimed method (which is denied), Applicants note that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Here, Applicants submit that there is nothing in the cited references that suggests they be combined. The Examiner urges that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a high concentration of antibody especially in the case of subcutaneous injection because the skilled artisan would have been aware that degradation of some of the injected antibody by that route of administration would limit the effective amount." While no reference is relied upon to support this position, Applicants submit that if it was the case that SQ administration was known to result in degradation of some of the injected antibody by that route of administration, this would have been a reason why the skilled person would not have modified the teaching of Davis (which concerned IV administration of the anti-IgE antibody). Moreover, the only reference that mentions – in passing – SQ administration is Arakawa, but that concerns a totally different antibody and disease from that claimed herein. Moreover, there is no guidance in Arakawa or the other cited art as to how to generate a formulation for SQ administration. Thus, Applicants respectfully submit that a *prima facie* case for obviousness can not be made out where, as here, the motivation to combine the teachings of the references is absent from the prior art.

Applicants submit that the present invention is not obvious over the cited references, and reconsideration and withdrawal of the Section 103 rejection is respectfully requested in view of the above amendments and remarks.

**Section 103 – Froehlich, Arakawa, Coval and Cleland**

Claims 37-39 and 44-49 are rejected under 35 USC Section 103(a) as being unpatentable over Froehlich *et al. J. Allergy Clin. Immunology* Abstract 863 (Jan., 1995) in view of Arakawa, Coval and Cleland.

Froehlich is said to teach administration of anti-IgE antibody to patient with IgE-mediated allergic disease, SQ or IV.

Applicants submit that the presently claimed invention is patentable over the cited art.

Applicants have discussed above the teaching of Arakawa, Coval and Cleland. As recognized by the Examiner, the Froehlich abstract does not teach the concentration of antibody recited in the instant claims. As explained above, the present invention involved, at least in part, the recognition of the desirability of the presently claimed high anti-IgE antibody concentrations for SQ administration (not disclosed or alluded to in Froehlich or the other references). In addition, the present application provides an enabling disclosure as to the development of a high concentration anti-IgE antibody formulation that is, surprisingly, stable in spite of the high antibody concentration in it, and, moreover, safe and effective for SQ administration to patients for treating IgE-mediated allergic disease. While the Examiner urges that the "patentability of a product does not depend on its method of production," Applicants point out that the claims herein are not "product" claims, rather they are "method" claims, and in order to anticipate or render obvious a claimed invention, the prior art must contain an enabling disclosure. Applicants submit that the Froehlich abstract does not contain an enabling disclosure as to therapy with a formulation comprising an anti-IgE antibody in an amount in the range from 80 mg/mL to about 400mg/mL. Hence, Applicants submit that the presently claimed invention is patentable over the cited art.

Furthermore, in order to make out a prima facie case of obviousness, the PTO much show where both the teaching or suggestion to make the claimed combination and the reasonable expectation of success can be found in the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that such has not been shown here and for this additional reason, Applicants respectfully submit that the rejection should be reconsidered and withddrawn.

Applicants submit that the presently claimed invention is patentable over the cited references. Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

**Section 103 – Chang 2, Arakawa, Coval and Cleland**

Claims 37-39 and 44-49 are rejected under 35 USC Section 103(a) as being unpatentable over US Patent No. 5,543,144 (Chang 2) in view of Arakawa and

Coval and Cleland.

Chang 2 is said to disclose treatment of patients afflicted with IgE-mediated allergy in amounts sufficient to eliminate substantially IgE-producing cells and to deplete IgE, i.e. 30-500mg/dose/subject in humans. Chang 2 is said to further disclose SQ or IV injection of an anti-IgE antibody.

Applicants submit that the presently claimed invention is patentable over the cited art. Arakawa, Coval and Cleland have been discussed above. The additional reference, Chang 2, is acknowledged by the Examiner to fail to teach a formulation comprising an anti-IgE antibody in the range from 80 mg/mL to about 400mg/mL. As noted above, the inventors of the present applications first recognized the desirability of such high anti-IgE antibody concentrations for SQ administration, something which was not taught for an anti-IgE antibody formulation in Chang 2 or the other cited references. In addition, the inventors actually made and tested a high concentration anti-IgE antibody formulation that was, surprisingly, stable despite the high antibody concentration in it, and, also, safe and effective for SQ administration to patients for treating IgE-mediated allergic diseases. See, especially, Example 2 of the present application. Such an enabling disclosure is lacking from the cited art.

The other references fail to supply the deficiencies of Chang 2. Coval only teaches gamma globulins at 50mg/mL. Cleland is concerned with rhGH and rIFN-γ, as opposed to an antibody, much less an anti-IgE antibody. It is not predictable from Cleland whether a stable antibody formulation suitable for SQ administration can be prepared. There is no motivation in Cleland to formulate an antibody, nor is there motivation to administer the controlled release formulation therein SQ.

In addition, Applicants submit that the Examiner has not shown where the teaching or suggestion to combine the various references and the reasonable expectation of success can be found in the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Since this is required for a *prima facie* case of obviousness, Applicants submit that this further demonstrates that the presently claimed invention would not have been obvious from the cited references.

Reconsideration and withdrawal of the Section 103 rejection is respectfully

requested in view of the above amendments and remarks.

**Section 103 - Shields, Arakawa, Coval, and Cleland**

Claims 37-39 and 44-49 are rejected under 35 USC Section 103(a) as being unpatentable over Shields *et al. Int. Arch. Allergy Immunol.* 107:308-312 (1995)in view of Arakawa, Coval and Cleland.

Shields is said to disclose treatment of patients afflicted with IgE-mediated allergy at doses up to 50mg/kg in monkeys and at 0.5 mg/kg in humans of anti-IgE antibody in single or multi-doses, SQ or IV.

Applicants submit that the presently claimed invention is patentable over the cited art. Arakawa, Coval and Cleland have been discussed above. The additional reference, Shields, is acknowledged by the Examiner to fail to teach a formulation comprising an anti-IgE antibody in the range from 80 mg/mL to about 400mg/mL. As noted above, the inventors of the present applications first recognized the desirability of such high anti-IgE antibody concentrations for SQ administration, something which was not taught for an anti-IgE antibody formulation in Shields or the other cited references. In addition, the inventors developed a high concentration anti-IgE antibody formulation that was, surprisingly, stable in spite of the high antibody concentration in it, and, moreover, safe and effective for SQ administration to patients for treating IgE-mediated allergic diseases. See, especially, Example 2 of the present application. Such an enabling disclosure is lacking from the cited art.

As to the other references, even when combined with Shields, Applicants submit they do not render obvious the presently claimed invention. Coval only teaches gamma globulins at 50mg/mL. Cleland is concerned with rhGH and rIFN-γ, as opposed to an antibody, much less an anti-IgE antibody. It is not predictable from Cleland whether a stable antibody formulation suitable for SQ administration can be prepared.

In addition, in view of *In re Vaeck* and other cases, Applicants point out that it is incumbent on the office to demonstrate where the motivation to combine the teachings of the cited references can be found in the prior art. This, in Applicant's submission, has not been done. The Examiner opines that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a high concentration of antibody

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especially in the case of SQ injection because the skilled artisan would have been aware that degradation of some of the injected antibody by that route of administration would limit the effective amount. No reference or evidence is cited to support this assertion by the Examiner. In any event, even if this was shown to be the case, this still fails to demonstrate that the skilled person would have known from the cited art to make a formulation comprising an anti-IgE antibody in the range from 80 mg/mL to about 400mg/mL, and administer such a formulation SQ. Moreover, it fails to provide the required reasonable expectation that such a formulation would be stable in spite of the high antibody concentrations therein, much less that such a formulation would be safe and effective for SQ administration.

Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

Respectfully submitted,
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